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**A DISCRETE-EVENT SIMULATION MODEL OF  
MYOCARDIAL ELECTRICAL ACTIVITY:  
MATHEMATICAL ELECTROPHYSIOLOGY**

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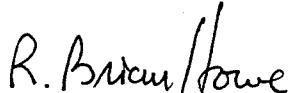
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## 1 Introduction

Beginning in 1984 and extending into 1993, the USAF Armstrong Laboratory, through the Aerospace Medicine Directorate's Clinical Sciences Division, supported a unique effort in the model-based derivation of ECG diagnostics; the purpose of this effort was development of an enhanced ECG lead set and diagnostic criteria for detection of asymptomatic coronary artery disease (CAD) in USAF aircrew members. This work was principally focused in a contracted effort; Dr. Ronald H. Selvester (University of Southern California, Rancho Los Amigos Campus, and Memorial Heart Institute, Long Beach Memorial Medical Center) was the principal investigator, and Col. Gil D. Tolan (retired) was the original in-house project scientist. Joseph C. Solomon, the co-investigator and Dr. Selvester's long-time collaborator, was responsible for the development of the simulation software, as well as other technical matters, as required by the contract.

Dr. Selvester's work on the development of ECG diagnostic criteria has been based on the premise that an advantage could be gained by exploiting knowledge derived from computer simulation of the underlying cardiac electrical phenomena ([1] and references therein). Validation of his work on the localization and quantification of infarct, using criteria developed with such an approach, is well documented (references in [1], [4], and, e.g., [5]). The effort supported by the Clinical Sciences Division was intended to generalize his work on diagnostic criteria for infarct to the case of ischemia.

As part of this effort, Selvester and Solomon developed a computerized forward model of the ECG; it consisted of a ventricular electrophysiology (depolarization and repolarization) model, a multiple fixed-dipole equivalent cardiac source model, a torso transfer impedance model, and a model for derivation of various ECG lead systems from the source and torso models. Details of Selvester and Solomon's models can be found in their 1985 Technical Report [1].

Due to funding limitations, their models were not developed to the extent that was originally intended, and did not incorporate the simulation of many aspects of normal and ischemic electrophysiology which were thought to be important to an understanding of ECG diagnostics for asymptomatic CAD. Work Unit 77552720 was instituted primarily as a response to this situation, to provide a channel through which in-house work could be performed to enhance the contract models so a more comprehensive set of model-based hypotheses could be generated. The two principal tasks set forth at the inception of the work unit were to:

- Generalize the simulation model of ventricular electrical activity, and
- Stabilize the numerical behavior of the torso transfer matrix computation.

These two issues were addressed in a natural progression. Our initial work focused on development of an enhanced simulation of the ventricular depolar-

ization and repolarization processes which would have the capacity to simulate inhomogeneous and anisotropic conduction, re-entry into the Purkinje system, and dispersion of refractoriness in a way that could be easily adapted to include other electrophysiological phenomena which might arise as subjects of interest. The resulting simulation is phenomenological rather than mechanistic, requiring explicit specification of action potential components and conduction velocities throughout the ventricles; on the other hand, one has complete control of the simulation scenario.

As an outgrowth of an attempt to validate the ventricular model in terms of internal consistency with the entire ECG forward model scheme, we began work on the problem of stabilizing the torso transfer matrix computation, but this work was not completed.

In this technical paper, we discuss only our discrete-event simulation model of myocardial electrical activity. It is the only complete component of the work intended to be done under the work unit, and its application provided the impetus for other work that was attempted but not completed. Following a description of the simulation model, we describe the general results and conclude with a discussion of how this work relates to broader issues, as well as "lessons learned" from the effort.

## 2 The Discrete-Event Simulation Model

Like Selvester and Solomon's model of the heart, our model is a "simulation model" rather than as a "mathematical model" because it is *algorithmic* in nature, as opposed to mathematical. In other words, it is defined by the algorithms embodied in the simulation software rather than by a set of partial differential equations, as would be the case if we were modeling the ion kinetics. Likewise, it is a simulation of bioelectric phenomena rather than a model of electrophysiological mechanism.

The core of Selvester and Solomon's model, as well as ours, is the algorithm for computing the depolarization wavefront. Conceptually, Selvester and Solomon base their algorithm on Huygens' method of wavefront propagation [1]. In this method, the wavefront at time  $t_2$  is formed from the wavefront at a previous elementary time step,  $t_1$ , by forming the envelope of elementary wavelets emanating from each point of the wavefront at time  $t_1$ , where the elementary wavelets depend on a uniform, direction-independent conduction velocity. Our model is conceptually based on a generalization of Huygens' method in which each point of the underlying space (e.g., the ventricular myocardium) possesses an "indicatrix" of direction-dependent conduction velocities [6]. In both models, the cells are conceived of as being uncoupled during repolarization.

A major goal of our work was to maintain complete input-output data compatibility with the Selvester-Solomon simulation, while generalizing the class of electrophysiological phenomena that could be simulated. Data compatibility was achieved, but generalization of the simulation required a complete redesign of the software.

**Acknowledgement of Data Source.** All of the input data for our model was provided under contract along with the Selvester-Solomon simulation software. All of the model elements described below were implemented using this data, which was developed by Joe Solomon under the guidance of Dr. Selvester. Additional details on many of these data elements can be found in the technical report by Selvester and Solomon [1].

### 2.1 Anatomical and Electrophysiological Structure

The global, or large-scale, anatomical structure is defined by a digital representation of an actual ventricular geometry, at diastole, obtained under contract from Selvester and Solomon [1]. Global coordinates are assigned to the points of the geometry by setting it in the positive octant of the conventional three-dimensional, orthogonal, right-handed x-y-z coordinate system with axes scaled to measure in 1mm units, and with the z-axis measuring the extent from apex to base. So defined, the geometry fits easily within a  $128\text{mm}^3$  cube. In its primitive form, this geometry is defined by occupancy of points on the three-dimensional integer lattice ( points  $(i, j, k)$ , where  $i, j$ , and  $k$  are integers) within this cube.

Conceptually, we take these occupied points to represent the center points of 1 mm<sup>3</sup> blocks of cardiac tissue which make up the elementary cellular units of the model.

The ventricular structure is decomposed into two basic types of spatially discrete cellular units: Purkinje units and myocardial units. Purkinje units represent blocks of tissue with a dense Purkinje fiber distribution and myocardial units represent blocks predominantly incorporating myocardium. Each cellular unit is associated with a set of electrophysiological parameters and properties which are used in the simulation to reproduce desired bioelectric phenomena. The geometric discretization embodies an implicit assumption that the small anatomical region represented by each cellular unit is homogeneous enough that the corresponding parameters and properties of its biological constituents does not vary significantly from the "average values" assigned to the cellular unit.

The ventricular tissue model is represented in the simulation model by two data structures:

- A 128 × 128 × 128 array, each element of which contains a pointer. If the element corresponds to coordinates for a ventricular cellular unit, the pointer indicates an element in an array of data structures containing representations for the electrophysiological components of the cellular units. If the element does not correspond to coordinates for a ventricular cellular unit, the pointer indicates a "null" value.
- An array of data structures containing the specifications for the cellular units in terms of electrophysiological components, such as conduction properties and action potential parameters.

The rationale for this dual structure is that the full ventricular geometry contains 287,140 myocardial units and 56,090 Purkinje units, for a total of 343,230 cellular units, comprising approximately 16.4% of the 128<sup>3</sup> coordinate array. Assignment of a data structure to each point of the array would have resulted in an enormous, unnecessary consumption of computer memory. In fact, an earlier design incorporating such an assignment was tested on the Digital Equipment Corporation (DEC) VAX computers available for the simulations. The intense referencing of this aggregate data structure by our simulation algorithm produced severe memory paging problems in the VAX computer, resulting in an extremely impractical program runtime.

The data structure for each cellular unit contains values for the following electrophysiological components:

- Cell Type - Purkinje or myocardium.
- Conduction Velocity Indicatrix - specification of possibly direction-dependent conduction velocity, relative to the center-location of the cellular unit, in a way that is commensurate with the depolarization wave propagation

algorithm (see below). The specification in terms of conduction velocity is replaceable by fiber orientation and conductivity tensor, depending on the algorithm for computing propagation.

- Action Potential Waveform - either a pointer to a regional action potential parameter set or an individual set of action potential parameters, depending on the configuration, or objective, of the simulation. The action potential function is a continuous-time version of an ad hoc formula derived by Joe Solomon [1]. Its functional form is fixed for all cells, but its morphology can be varied by modulation of a number of parameters. The (default) distributions of these parameters, across the cellular units, are specified to approximate the spatial distribution of action potential morphologies in a normal human heart. These parameters include
  - Resting potential,
  - Rise-time of action potential,
  - Depolarization potential,
  - Absolute refractory period, and
  - Recovery rate.
- Action Potential Firing Time - the time, in milliseconds(ms), at which the cellular unit was last activated. Time is typically measured in reference to the first activation of a Purkinje or myocardial unit being designated as time zero (0). The simulation begins with the action potential firing time of all cellular units set to a common negative value such that they are in a normal resting state at time zero.

**Note.** In the following, for the sake of simplicity, we use the term “cell” instead of “cellular unit” to represent the macroscopic block of tissue previously described.

## 2.2 Propagation of the Depolarization Wavefront and Repolarization

Briefly, the simulation model begins with initial activation of bundle entry sites among the cells designated as Purkinje type. From this beginning, activation is propagated by electrotonic interaction between cells, as well as by additional bundle entries, until the entire ventricular mass is activated. Activation of a cell marks the temporal starting point for its associated action potential waveform, from which the course of repolarization is computed. The complexity in this process arises from computation of the depolarization wavefront.

The initial activation of bundle entry sites results in the formation of an initial depolarization wavefront. Activation times are computed for all repolarized cellular units within the 26 cell neighborhood of each of the cells in the

wavefront. The algorithm for computation of the activation times accounts for the effects of a number of anatomical and electrophysiological phenomena, as described below. During the computations for each wavefront, the neighboring cells are "scheduled" and "rescheduled" to insure that their activation times are the earliest times at which propagation would occur relative to the wavefront. The next wavefront consists of all those cells having the "next" activation time appearing in the activation-event scheduling structure. In this process, there is no pre-specified minimal time step. The interplay of Purkinje and myocardial conduction velocities with three-dimensional geometric relationships results in a dense structure of activation times which have to be managed with special data structures.

Our simulation model has the potential of reproducing the following phenomenological features of myocardial activation:

- **Electrotonic Interaction Between Cellular Units.**

Propagation of the depolarization wavefront proceeds from cell to cell, with an activated cell propagating the wavefront to a neighboring cell at the end of a time interval depending on the conduction velocity at the activated cell and the distance to the neighboring cell.

The neighborhood of a given cell consists of all cells whose centers are strictly less than 2 mm from the center of the given cell. Defined in this way, the neighborhood of a given cell can be visualized as containing all cells whose centers lie on a face, on an edge, or at a vertex of the cube centered at the given cell and having edges of 2 mm in length. Thus, the neighborhood of a cell contains at most 26 other cells, depending on how many of the surrounding lattice points are occupied by cellular units and how many surrounding lattice points correspond to the space outside of the heart.

In the case of a homogeneous, isotropic conduction velocity, of magnitude  $v$ , within the region of computation, the propagation time from an activated cell located at coordinate vector  $\vec{x}$  to a neighboring cell located at coordinate vector  $\vec{y}$  is given by the distance between the cells divided by the magnitude of the velocity:

$$T(\vec{x}, \vec{y}) = |\vec{y} - \vec{x}|/v.$$

- **Inhomogeneity in Cell Type.**

There are two types of cells in our model, resulting in three different possible interactions: Purkinje-Purkinje, Purkinje-myocardium, and myocardium-myocardium. In principle, propagation between cells of different type should be modeled differently than propagation among cells of the same type. However, in our simulation, the Purkinje cellular units are taken to model an averaged behavior for myocardium which is densely interlaced

with Purkinje fibers. Therefore, a Purkinje-to-myocardium interaction (and vice versa) is defined as equivalent to a myocardium-to-myocardium interaction. On the other hand, we follow Selvester and Solomon in specifying that the propagation in a Purkinje-Purkinje interaction be three times faster than among myocardial cells. (This ratio varies significantly among models reported in the research literature.) Consequently, we model Purkinje cells with a conduction velocity indicatrix of the same relative magnitude as myocardium, but increase its magnitude by a factor of three when applying it to a neighboring Purkinje cell.

- **Inhomogeneity in Conduction Velocity.**

Deviations in conduction velocity are known to occur with ischemia; thus, an essential feature of the model is the ability to account for inhomogeneities in conduction velocity within the myocardium.

The structure of our tissue model allows us to specify a different conduction velocity indicatrix for each cell in the ventricular anatomy. Our simulations took the form of either scaling the normal myocardial conduction velocities in a region by a fixed factor (e.g., one-half) or randomly modulating the normal conduction velocities in a region.

- **Fiber Anatomy and Anisotropic Conduction.**

Individual myocardial cells are elongated and connected in a roughly end-to-end manner to form fibers, which in turn serve as components of larger structures. These structures are organized into a complex architecture which is optimized, especially in the left ventricle, for efficient contraction and emptying of the ventricular chambers.

The fiber structures of the heart also play a significant roles in the formation of electrophysiological phenomena. The special nature of the junctions between cells in a fiber results in higher electrical conductivity along the length of the fiber than across it. As a result, the conduction velocity of the depolarization wavefront is directionally dependent, or anisotropic, depending on the local average fiber direction.

At the global level, the structure remains complex, but generally results in a circumferential conduction that is faster than the transmural conduction. It is thought by many researchers that the anisotropic nature of the conduction does not affect the normal activation sequence for the ventricles, because the propagation of the depolarization wavefront generally takes a transmural course from endocardium to epicardium. On the other hand, the anisotropic nature of the conduction velocities would seem important in accurately modeling cases in which the depolarization wavefront does not propagate transmurally in a uniform manner, such as in some cases of infarct and ischemia, bundle branch blocks, and many arrhythmias.

Because of the simulation model's organization, the mechanism of conduction can be specified by the user in a manner most convenient for the purpose at hand. In most published simulation studies involving anisotropic conduction ([7] and references therein), actual or approximate fiber directions are used to define the directional dependence of electrical conduction, which is in turn used to define conduction velocities in some ad hoc manner. We took a simpler approach and worked directly in terms of conduction velocities. The natural way to define a fiber-based conduction velocity is to specify a conduction velocity along the length of the fiber and a circumferential velocity along any orthogonal axis. From this, a fiber-based conduction velocity can be computed for any direction. On the other hand, we had already defined a global coordinate system for specifying the location of cells, so we preferred to define our conduction velocities directly in terms of the same global coordinate axis directions.

Specifically, the conduction velocity indicatrix for a given cell at coordinate vector  $\vec{x}$  can be specified by a velocity vector,  $\vec{v}$ , which might be formed by projecting the longitudinal and circumferential components of a fiber-based conduction velocity onto rectangular axes originating at  $\vec{x}$ . Then, the propagation time from the given cell to a neighboring cell centered at  $\vec{y}$  is defined as the distance between the two cells divided by the magnitude of the component of the conduction velocity projected onto the direction indicator from  $\vec{x}$  to  $\vec{y}$ :

$$T(\vec{y}, \vec{x}) = \frac{|\vec{y} - \vec{x}|}{\left| \vec{v} \circ \frac{\vec{y} - \vec{x}}{|\vec{y} - \vec{x}|} \right|},$$

where “ $\circ$ ” denotes an inner product of vectors.

- **State-Dependent Propagation between Cells.**

The excitability (susceptibility to depolarization) of a myocardial cell is dependent on its “refractory state,” which can be thought of as a state corresponding to certain conditions at the ionic level. In the fully repolarized or resting state, the cell is capable of participating in normal ionic current flow, with the capability for normal conduction and production of a normal action potential. Cell depolarization and recovery follows a sequence of ionic current flows which are interruptable only under certain conditions. When the action potential of a myocardial cell is in the plateau phase of its waveform, it is in an “absolute refractory state” and is not interruptable. When it is repolarizing in the downward slope of the waveform, however, the underlying ionic current flows are partially interruptable, and depolarization can again be achieved. In this “relative refractory state”, the response is muted, with decreased conduction velocity and distortion of the resulting action potential.

In our model, this phenomenon is simulated by modulating the conduction velocity between an activated cell and a neighboring cell according to the refractory state of the neighboring cell. If the neighboring cell is completely repolarized, then the propagation time between the cells is computed using the normal conduction velocity indicatrix of the activated cell. If the neighboring cell is in an absolute refractory state (i.e., within the absolute refractory period as specified for its action potential waveform) it cannot be reactivated, so the conduction velocity between the cells is set to zero. If the neighboring cell is in a relative refractory state (i.e., beyond its absolute refractory period, but not yet fully repolarized) then the conduction velocity indicatrix of the activated cell is scaled by the following ratio:

$$\frac{\text{Action Potential} - \text{Depolarization Potential}}{\text{Resting Potential} - \text{Depolarization Potential}}.$$

We used this scheme primarily for proof of concept. More realistic functional relationships can be found by consulting the research literature on refractory states of excitable cells.

In our implementations, we only modulated the conduction velocities, and did not attempt to modulate the action potential morphologies, although its incorporation into the software should be easily managed for a model specified in terms of functional relationships.

This is not the whole story. Of particular importance in modeling arrhythmias, as well as exercise effects (there are more difficult problems in this case), is the dependency of conduction and action potential morphology on the frequency of activation. General functional forms for some of these dependencies are available from the research literature, but we did not explore such a capability as part of our work.

**The Simulation Algorithm.** The main data components and behavioral elements of the simulation model have been described above. We will now present a succinct description of the most general simulation algorithm we implemented. Because of the admitted provisional nature of some of the modeling components, this should be considered more of an example than a definitive exposition.

Let  $VM$  denote the ventricular geometry, including both Purkinje and myocardial cells, and let  $WF$  denote the depolarization wavefront. *SCHEDULE* is a data structure which is used to accumulate the “next” depolarization wavefront by managing “predicted” firing (depolarization) times for cells neighboring the wavefronts, and updating them as necessary. The simulation is initialized by constructing the ventricular geometry and array of cell parameters, and by initializing *SCHEDULE* with a set of locations and firing times for entry sites of the conduction bundles into the Purkinje system. In the following example,

we shall reference a cell in the ventricular structure by its location coordinate vector (e.g.,  $\vec{x}$ ).

The basic algorithm is as follows:

- Initialize the simulation.
- Do the following, until the myocardium is fully repolarized:
  - Extract the next wavefront,  $WF$ , at time  $T$ , from SCHEDULE.
  - Propagate the wavefront,  $WF$ :

For every  $\vec{x}$  in  $WF$ , compute the local wavelet propagation:

- \* Find the neighborhood of  $\vec{x}$ ,  $N(\vec{x})$  in  $VM$ .
- \* Determine the tissue type of  $\vec{x}$ ,  $TYPE(\vec{x})$ .
- \* for every  $\vec{y}$  in  $N(\vec{x})$ :
  - Determine the tissue type of  $\vec{y}$ ,  $TYPE(\vec{y})$ , and compute the type factor  $TF$ , where  $TF = 3$  if both  $TYPE(\vec{x})$  and  $TYPE(\vec{y})$  are Purkinje, and  $TF = 1$  otherwise.
  - Determine the state of  $\vec{y}$ :

$$STATE(\vec{y}) = \frac{AP(\vec{y}, T) - V_d}{V_r - V_d},$$

where  $AP(\vec{y}, T)$  is the action potential voltage of cell  $\vec{y}$  at time  $T$  measured relative to the last action potential firing time for  $\vec{y}$ ,  $V_d$  is the depolarization potential of  $\vec{y}$ , and  $V_r$  is the resting potential of  $\vec{y}$ .

- Compute the conduction velocity at  $\vec{x}$  in the direction of  $\vec{y}$ , as dependent on cell type and refractory state:

$$V(\vec{x}, \vec{y}) = TF \times STATE(\vec{y}) \times \left( \vec{v} \circ \frac{\vec{y} - \vec{x}}{|\vec{y} - \vec{x}|} \right).$$

- Compute the predicted firing time,  $FT$ , of  $\vec{y}$ :

$$FT = T + \frac{|\vec{y} - \vec{x}|}{V(\vec{x}, \vec{y})}.$$

• Schedule  $\vec{y}$  to fire at time  $FT$ :

*PUSH\_SCHEDULE*( $\vec{y}$ ,  $FT$ ).

Note that the entire section following “For every  $\vec{x}$  in  $WF$ :” is encapsulated in a single subroutine of the simulation software, acting on the tissue model, and could easily be replaced by more general functions.

### 2.3 Software Engineering

There are two computational aspects of our simulation software which are worth noting, although their discussion is not essential for understanding of the conceptual model itself.

First, the simulation model was initially regarded as being provisional. We expected to upgrade various components as time passed, so we constructed the software to facilitate such occurrences by modularizing at the level where we expected the changes to take place. This led us to consider the simulation implementation in terms of correspondences between the conceptual components of the model and data objects in the software; in other words, form the viewpoint of an object-oriented design philosophy (see [8] and references therein). On the other hand, to ensure software compatibility with the contracted work of Selvester and Solomon, we were implementing our simulation in Fortran 77, which does not support object-oriented programming techniques. Therefore, we adopted Fortran *programming conventions*, some of which were drawn from the literature ([9], [10], [8]), to implement a weak form of data abstraction (encapsulation of data and the subroutines that operate upon it). This approach was adequate for our needs, and considered a success; it enabled us to make several major changes to specific software components during development without requiring significant changes to other components. In terms of the conceptual components of the model, another advantage was the resulting structural coherence of the software, which made the code easier to understand.

The second computational point of interest is in our choice of event-scheduling methodology. While there have been a number of reports in the literature of simulations based on the methodology of Selvester and Solomon’s early work (recently: [7], [11]), few simulations of cardiac electrophysiology have been implemented using a discrete-event simulation approach. The discrete-event simulations that have been reported are usually implemented using specialized data structures and algorithms for managing the timing of cell activations ([12], [13]). We wanted to avoid such an approach because it seemed to inhibit flexibility for future software evolution and would place the work outside of the mainstream of simulation technology. Such a decision, however, left us needing methods to efficiently handle the scheduling of many thousands of events.

Using standard linked-lists was untenably slow, so we reviewed the literature and found a study by Jones which reported empirical comparisons of priority-

queues [14]. The best performance for very large queues, under most of the test models, was obtained by the splay trees of Sleator and Tarjan [15]. The implementation of splay tree scheduling algorithms resulted in much faster simulations, which could be completed overnight when run in batch mode on the available DEC VAX computers. The details of the basic algorithm are complex, and would best be attained from the paper of Sleator and Tarjan, where they are presented in a "pseudocode" format. We only implemented the most basic version, although there are a number of possible optimizations cited in their paper.

Our initial implementation used splay trees for managing events using two search keys: first events are ordered according to a time key, and then for each time they are ordered according to a coded representation of the cell's spatial coordinates in the  $128^3$  lattice. This algorithm was elegant in structure, but required additional computations for the coding and decoding of coordinates. Our final method was a hybrid approach, using a splay tree for management of the time key, and time-indexed bins, implemented as linked lists, to index the cells scheduled to fire at each time key. This latter component was derived from a suggestion offered independently by Col. Gil Tolan and Dr. Sherwood Samn, and represents a successful trade-off of computer memory for speed of computation.

### 3 Results

The simulation model was first tested by running simulations for two-dimensional arrays of the myocardial cellular units to confirm that the algorithmic machinery for computing inhomogeneous and anisotropic conduction would behave as intended. A number of simple conduction scenarios were fabricated to exercise the algorithm. The results were displayed graphically on a Tektronix 4111 computer graphics terminal.

Next, we tested the full three-dimensional ventricular geometry model. The output from these simulations was either an interactive computer graphics display or a batch-computed animation sequence for display on a Siemens DELTAVision medical imaging system. The display format was basically an enhanced version of the design developed under contract by Selvester and Solomon (see [16] for an example). Using these displays, the progression of depolarization and repolarization of the ventricles could be directly observed. For this type of simulation, in which the results of the computation are distributed in space as well as in time, computer graphics representation of the results seems to be one of the few direct ways to confirm correct behavior of the model. We are unable to include images from the computer graphics displays in this report.

Our primary design constraint in developing this simulation was compatibility with the modeling framework of Selvester and Solomon. Our first test using the ventricular geometry was duplication of the simulations of their ventricular model (homogeneous, isotropic conduction throughout the myocardium, with conduction in the Purkinje system specified as three times faster), for normal and infarct cases. This was accomplished by setting our model's conduction parameters at equivalent values to those implicitly found in their model. We found excellent agreement between the two models, as expected, since Selvester and Solomon's model served as the default behavior of our model.

To test the mechanism for computing inhomogeneous conduction in its intended setting, we used the infarct geometry from Selvester and Solomon's model to define a region of slowed conduction (as in a hypothetical ischemic region) in the ventricular myocardium. For test purposes, the slower conduction velocity was simply one-half normal velocity. The computer graphics display revealed the expected lag in the depolarization waveform as it passed through the affected region.

Finally, to further test inhomogeneous conduction, as well as propagation between different cell types, we simulated a full right bundle branch block with activation originating in the left bundle, as well as a similar simulation for the case of full left bundle branch block. The depolarization waveform proceeded as expected, passing across the septum and re-entering the Purkinje network below the block.

These scenarios are simplistic, but are merely intended to be tests and demonstrations of the simulation software capabilities. The realism of the simulations would be expected to increase with increasing realism in the specification

of input parameters. However, we were unable to attempt to refine these parameters.

## 4 Discussions

### 4.1 The Simulation Model in a Broader Context

Early in the development of our simulation model, we began to view it as more of a framework for model implementation than as a single fixed model. We expected to change the model's inner mechanisms as it was applied to the analysis of increasingly detailed questions regarding the electrocardiology of ischemia. In this sense, the rudimentary form of data abstraction which we applied in development of our software was important. It explicitly organized the software into a framework where components could be changed with little impact on the rest of the program.

In light of its extendibility, we consider this simulation framework to be as capable as any phenomenological simulation model of the ventricles reported in the research literature. As a specific model of ventricular electrical activity, it lacks a complete specification of realistic electrophysiological parameters, as well as complete development of certain functional characteristics of propagation, such as frequency dependence of conduction velocity.

We also preferred to view this simulation as a framework rather than a fixed model because the simulation of "abnormal" electrophysiology in terms of macroscopic phenomena is fundamentally flawed. Our development of a discrete, phenomenological model was initially mandated by a desire for compatibility with Selvester and Solomon's work, as well as by the fact that it was simply what we understood how to do at the time. As our perspective evolved and our knowledge grew, we began to more fully appreciate the advantages of directly modeling the biophysical mechanisms underlying the phenomena. In fact, an approach to the problem on the biophysical level is essential if one wishes to begin to understand what is happening during ischemia, during exercise, or during interactions with mechanical fields (e.g., myocardial contraction with and without  $+G_z$  stress). On the other hand, simulation in terms of biophysics is not tenable at the scale of the ventricular muscle mass. In fact, simulations using detailed ionic current models at the scale of the whole heart are beyond the capabilities of current supercomputers for known methods of integration.

Consequently, strategies which balance the need for electrophysiological detail against the computational burden of simulating phenomena at the scale of the ventricular muscle mass are needed. Discrete, phenomenological simulation may yet be useful in the development of such strategies. Specifically, studies involving detailed biophysical models can be used to derive data and phenomenological models of dynamics for use in discrete-event simulations on the large scale. After realizing this at a fairly early stage, and beginning work in this context, we were pleased to find these sentiments reflected in comments in the recent paper of Manor, et al., on propagation of neuronal action potentials [17]:

... it is clear that the [detailed] modeling approach is limited when

one wishes to model large ... systems for long periods of time ... In such cases some simplifications are necessary. ... [One] approach, ..., is to use parallel machines, each handling only a part of the simulated system ... [Another] approach, ..., is to move to a higher and much faster level of modeling, the event-driven or "state-machine," scheme. In order to retain the essential features of the modeled system, the construction of this level of representation should be based heavily on the functional rules that were formulated as a result of detailed exploration of the [detailed] models.

Aside from the advantageous information yield of working with biophysical models, we were attracted to this complementary modeling paradigm because much of the detailed data needed for significant aspects of the ventricular simulation study was unavailable from the research literature and the (unproven) possibility that reasonable hypotheses about the missing data could be generated through biophysical simulations. Among our projected areas of study for this purpose were the action potential under myocardial ischemia and the self-organization of refractory period distributions and "cardiac memory" under various scenarios of conduction pathology (such as bundle blocks). However, the extent of our work in this area reached only so far as simulation of fairly simple ionic models on small two-dimensional arrays.

We have tried to describe our view of a proper framework for modeling and simulation of bioelectric phenomena; next, we would like to describe a formal framework for model-based derivation of diagnostic criteria.

## 4.2 The Work Unit in a Broader Context

As part of our efforts to understand how we could best enhance the ECG, we looked at the large-scale structure of the study design. The study could roughly be broken down into two components: the model-based generation of hypotheses about optimal lead systems and diagnostic criteria, and clinical investigation and validation of these hypotheses. While the clinical aspects of the study were clearly outside the scope of our in-house efforts, it became our view that the model-based hypothesis generation component of the study could have benefited from a more formal approach to its design.

In particular, ECG diagnostic criteria of the type sought in the study basically consist of rules for interpreting the electric potential measurements in various combinations of ECG leads (e.g., see [16]). Ischemic electrophysiology can be conceptually modeled as a perturbation of normal electrophysiology; diagnostic criteria for ischemia can be viewed as an attempt to create a mapping between perturbations from normal in ECG potentials and perturbations from normal in the underlying electrophysiology. The components of this mapping provide the proper abstractions to organize supporting modeling and simulation studies. This mapping can be formulated as a set of pairings between combi-

nations of perturbations in the electrophysiology of various coronary perfusion fields and responses in ECG lead sets or feature sets of interest.

Selvester and Solomon's original study design to enhance ECG diagnostics for ischemia included the generation of simulated ECG data for "all possible combinations" of ischemia at different levels of severity in all of the coronary perfusion fields [1]. This was to be followed by an analysis of the resulting simulation database to determine optimal electrode sites and diagnostic criteria for various combinations of ischemic perfusion fields.

Beside arguments concerning the scientific feasibility of specifying ischemic effects in the detail required by Selvester and Solomon's study design, we could see potential methodological problems. In particular, there was no specified approach for analyzing the simulation database, nor was there any formalism for managing the generation of simulation data in terms of the desired framework of abstractions. A natural approach to these types of problems can be found in the field of model-based diagnosis (a branch of the field of expert systems technology). The advantage of making this conceptual association is that the methods of model-based diagnosis are usually formulated directly in terms of the abstractions found at the diagnosis level. The models referred to in the term "model-based" are usually qualitative models describing the causal behavior of the system under diagnosis in terms of appropriate diagnostic abstractions.

An excellent prototype of this approach is found in the work performed by Bratko, et al., on their KARDIO system for automated diagnosis of cardiac arrhythmias [18]. Their work involved comprehensive simulation of many classes of arrhythmias, resulting in a large database of pairings between conditions in their heart model and corresponding ECG features in the form of logic formulas. Formal machine learning techniques were then applied to the database to extract diagnostic rules.

We believe that the simulation of basic electrophysiological scenarios can be combined with perturbative sensitivity analysis to derive a qualitative causal model of the ECG for ischemic heart conditions. The qualitative model would then provide a translation between fundamental mathematical models and the types of symbolic abstractions which can be utilized by model-based diagnosis techniques. This would facilitate the use of formal machine learning techniques in analyzing such simulation results and relating them in a well-defined way to diagnostic criteria.

The work of Selvester and Solomon on criteria for infarction and ischemia has shown that simulations studies can be used to help understand the structure of information in the ECG in terms of underlying biophysical principles and how this information can be used to enhance the diagnostic capabilities of the ECG. The ECG enhancement project as a whole, including both the contracted effort and this work unit, can be viewed, within the context of this emerging discipline of model-based enhancement of diagnostic systems, as an informal approach to "model-based knowledge acquisition" [18].

The review of Uckun [19] gives a broader overview of applications of model-

based reasoning in biomedicine, and the paper of Tong and Widman [20] provides a recent example of the application of this paradigm to ECG diagnostics. The paper of Siregar, et al., [21] indicates how more general models can fit into this framework, as well as a concise and lucid review of model-based diagnosis. As the literature shows, model-based reasoning is currently a very active subfield of artificial intelligence research, with potential for application to any diagnostic domain in which the system under diagnosis can be modeled by either quantitative or qualitative methods.

We also want to point out that a contemporary approach to the type of simulation study undertaken in the ECG enhancement effort would probably be quite different than that initiated in 1984. The complexities arising from the spatial distribution of parameters and the irregular geometries of anatomical domains would be addressed through the application of high-performance computers and tools such as magnetic resonance imaging (MRI), computer-aided design, and the finite element method ([22], [23]). The use of such tools is currently revolutionizing the discipline of biomedical modeling and simulation [22]. The recent work of Miller, et al., [24] may hint at a future where the anatomy and physiology of populations of individuals can be computationally modeled, and analyzed by machine-oriented techniques, to achieve an understanding of complexities that humans could not otherwise hope to comprehend.

### 4.3 Lessons Learned

In conclusion, we mention a few lessons learned from our general experience on this project.

**Computational methods for the simulation and analysis of spatially complex biological systems.** There are significant computational difficulties involved in simulating complex physiological interactions in systems where spatial extent is large with respect to the scale at which the biophysical interactions take place. Such problems can be computationally intractable unless simplifications can be made in the simulation requirements. Methods are needed which optimally preserve details of the underlying model versus computational requirements. Such methods could range over many different combinations of simulation software technique and high-performance computing. In dealing with systems whose components possess inhomogeneous characteristics, and are changing in various scenarios of interest, it is important to use methods which are not only computationally efficient, but also flexible. Finally, when the input set to a simulation includes complex spatial distributions of parameters, and the output set is of a similar nature, preparation and analysis of a systematic simulation study can become extremely cumbersome. Thus, there is a great need for computational tools allowing easy interactive generation, manipulation, and analysis of data defined over geometric domains in three dimensions.

**The uniqueness of Air Force requirements.** In recent years, there has been considerable activity in the modeling and simulation of cardiac electrophysiology by the mathematical biology and biomedical engineering communities. Most of this research, however, has been directed toward modeling the propagation of the depolarization wavefront in simplified models for the purpose of gaining insight into the nature of intra-myocardial arrhythmias.

Our interests, in the ECG enhancement effort, included those of the broader community, but extended beyond them. We were primarily interested in gaining insight into the detection of asymptomatic coronary artery disease via electrocardiography, as well as related issues such as modeling the electro-mechanical interaction. These objectives direct our attention to what is happening behind the wavefront of myocardial depolarization, for it is there that the most sensitive indicators of asymptomatic CAD arise, and it is there that the fine details of electro-mechanical interaction occur. Moreover, unlike much of the work on the modeling of arrhythmias, our program objectives required that we address the modeling of both the depolarization and repolarization processes over the entire muscle mass of the ventricles, with attention to the details of physiologically relevant inhomogeneities as they change in various scenarios of interest, such as rest, exercise, and +Gz stress.

These areas of emphasis stand apart from the concerns of the ECG and electrophysiology modeling communities at-large, and constitutes another demonstration that the Air Force presents requirements for biomedical investigation which may not be directly addressed by the general scientific community.

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